DONOVANOSIS

(Granuloma Inguinale, Granuloma Venereum)

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CONTENTS

		Page
1	Nomenclature and history	9
2	Features of distribution	12
3	Etiology	15
4	Epidemiology	21
5	Clinical features	24
6	Diagnosis	32
7	Treatment	40
Conclusion		44
References		44
Illustrations		47

ILLUSTRATIONS

1 Donovan bodies

2 Technique for obtaining smears for Donovan bodies

3 Hyperplasia of marginal epithelium with massive cellular reaction in corium

4 Acanthosis, with irregular elongation of rete pegs forming an interlacing network enclosing islands of cellular exudates

5 Histological section, showing intradermal abscesses

6 Granulation tissue showing plasma cells, lymphocytes, and scattered large mononuclear cells

7 Granulation tissue with marked hyperplasia of endothelial cells of the capillaries

8 Extensive fibrous tissue reaction with collections of cells in crevices of inter lacing strands of fibrous tissue

9 Histological section of granuloma inguinale showing pathognomonic cell stained with Delafield's haematoxylin

10 Early granuloma inguinale with daughter lesions often mistaken for condyloma lata

11 Multiple unbroken button like nodules on glans penis and inner lining of retracted prepuce

12 Granuloma inguinale of labia

13 Pseudo-bubo in groin

14 Early granulomatous ulcer on left side of prepuce

15 Early granulomatous lesion at frenulum

16 Extensive ulceration on dorsal aspect of prepuce and glans penis

17 Ulceration of labia minora, fourchet, and clitoris

18 Extensive granuloma of prepuce and glans penis extending upwards to both groins

19 Tendency of ulceration in female to spread downwards and backwards towards perineum and peri anal regions

20 Granuloma of inner side of lips and cheek secondary to genital disease

21 Fleshy type of granuloma of neck secondary to genital and buccal granuloma

22 Histological section of liver biopsy showing liver parenchyma cells containing Donovan organisms in varying numbers Dieterle stain

23 Histological section of liver biopsy showing capsulated organisms in the liver parenchyma cells Giemsa stain

24 Hypertrophic type of granuloma involving prepuce, right groin, and upper part of thigh in male

25 Hypertrophic type of granuloma involving major labia, clitoris, perineum, and peri anal region in female

26 Sclerotic type of granuloma in male, involving penis, penile shaft, and inner aspect of both groins

27 Destructive necrotic type of granuloma involving external genitalia perineum and peri anal region in female

28 Pseudo-elephantiasis of penis secondary to healed donovanosis

29 Pseudo-elephantiasis of external genitalia in female with long-standing donovanosis

30 Almost complete obliteration of pudendal cleft

31 Complete destruction of penis secondary to donovanosis

32 Pseudo-epitheliomatous hyperplasia grade II in a case of donovanosis

33 Pseudo-epitheliomatous hyperplasia grade III in a case of donovanosis

34 Extragenital granuloma inguinale of neck

35 Extensive granuloma of groins and of inguinal and pubic regions with deformity of penis (A) before and (B) after treatment with streptomycin

36 Successful transplantation of chemo-resistant donovanosis in groin and forearm of a volunteer

37 Granuloma inguinale of cervix (often mistaken for cervical carcinoma) before treatment with chloramphenicol

38 Granuloma inguinale of cervix (often mistaken for cervical carcinoma) after treatment with chloramphenicol

CHAPTER I

NOMENCLATURE AND HISTORY

The disease to be described in this study suffers from a multiplicity of names It is not surprising, therefore, that it has been confused by medical students and physicians, and even in medical literature and text books, with another disease—lymphogranuloma venereum or lymphogranuloma inguinale The subject of this study has been described under the following names

Serpiginous ulceration of the groin
Lupoid form of groin ulceration
Ulcerating granuloma of the pudenda
Granuloma inguinale
Granuloma venereum
Granuloma genito-inguinale
Granuloma venereum genito-inguinale
Infective granuloma
Granuloma inguinale tropicum
Chronic venereal sores
Ulcerating sclerosing granuloma

We agree with Marmell & Santora [55] that there is urgent need for a proper nomenclature for the disease, based upon the three fundamental etiological factors of (1) the discovery by Donovan [21] of the intracellular bodies constantly present in the lesions of the disease, (2) the establishment of the relationship of the intracellular bodies to the disease by Greenblatt and his associates,[32] who successfully reproduced the disease in a human volunteer by the subcutaneous injection of material rich in Donovan bodies, and (3) the successful isolation of the organism by Anderson,[3] who placed it in the new genus *Donovania*

Hence the name "donovanosis", suggested by Marmell,[54] seems to us an appropriate designation The advantages claimed for the new term are that it will rid the existing literature of the babel of names, stress the essential etiology of the disease, and give it a definite clinical entity and individuality On a personal note, the senior author (R.V R), as one of Donovan's former students, feels a certain satisfaction in the new designation, since it will remind present and future students and physicians

of the Madras Medical College and the associated General Hospital of Major Charles Donovan who, as professor and physician there, 48 years ago discovered and described the intracellular organisms from the buccal lesions of donovanosis in a patient under his care.

Donovanosis is a chronic, slowly progressive, mildly contagious disease of venereal origin, characterized by granulomatous ulceration of the genitalia and neighbouring sites, with little or no tendency to spontaneous healing. It was first recognized in India by McLeod[50] (1882), who described the condition under the name of "serpiginous ulcer" in Madras. Conyers & Daniels[15] (1896) reported cases from British Guiana as "the lupoid form of the so called groin ulceration", and gave a good clinical description of the disease. Galloway[25] (1897), under the term "ulcerating granuloma of the pudenda", gave a detailed description from a single case seen in London in a native of the West Indies. The credit for discovering and describing the presence of certain intracellular bodies in the exudate from an oral lesion of donovanosis in Madras belongs to Donovan[21] (1905), the co discoverer of the etiological agent of kala azar. Carter[9] (1910) gave an account of six cases of ulcerating granuloma of the pudenda seen by him in India, and described large mononuclear cells filled with bodies "resembling the gregariniform stage of a herpetomonas or crithidium". The description of the organisms by both Donovan[21] and Carter[9] resembles that of what are now known as Donovan bodies. Grindon[39] (1913) was the first to report cases from the United States of America. Goldzieher & Peck[26] (1926) gave a classical description of the disease, they claimed to have cultivated an intracellular capsulated bacillus and were the first

disease, in its clinical, cultural, pathological, diagnostic, and therapeutic aspects. In any historical review, the contribution of the workers of the Medical School of the University of Georgia, under the indefatigable leadership of Greenblatt, must have a large place. Pund & Greenblatt[64] (1937), under the title "specific histology of granuloma inguinale", described a large mononuclear cell, filled with intracytoplasmic cysts containing deeply staining bodies, which they called the "pathognomonic cell" of granuloma. Greenblatt and co-workers[32] (1939) reproduced the disease in a human volunteer by the subcutaneous injection of pus containing Donovan organisms in pure culture, aspirated from a case of unruptured pseudo bubo. The experiment was repeated successfully by transplanting subcutaneously, in another human volunteer, a piece of granulomatous tissue removed from a lesion in the same patient.

Many workers have claimed to have cultivated the organism of donovanosis in ordinary laboratory media, but their claims have not been confirmed.

Anderson[1] (1943) reported the successful cultivation of Donovan bodies in the yolk sac of a developing chick embryo, other workers have confirmed her claim

Secondary cultivation of the organism in artificial media after primary isolation in chick embryo was successfully carried out by Dienst et al[20] (1947), Dunham & Rake[23] (1948), and Dulaney et al[22] (1948) Within the past few years, the therapeutic effects of a battery of the newer antibiotics have changed the prognostic outlook of the disease

Donovanosis should be clearly distinguished from lymphogranuloma venereum, which is a virus disease affecting the lymphatic systems of the inguino genito-ano-rectal regions and associated with constitutional symptoms

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CHAPTER 2

FEATURES OF DISTRIBUTION

Geographical

The disease has a fairly wide geographical distribution in both hemispheres It is endemic in southern China, the East Indies, northern Australia, West and Central Africa, some countries of Central, South, and North America, and the West Indies Epidemics have been reported from South America and New Guinea In the USA, with its nation wide reporting of morbidity, it would appear that the disease is by far most prevalent along the Gulf of Mexico from Louisiana at the mouth of the Mississippi river eastward to the Atlantic, although about 25% of cases are reported from the rest of the country [12] In India the disease is endemic in the States of Madras and Orissa, with the greatest incidence in the districts along the eastern seaboard of the peninsula [56 57]

Recently Cutler *et al* [16] have brought to light another endemic focus of the disease among the Pahari hill dwellers of the Himachal Pradesh—a northwestern hill State of the Indian Republic In a limited survey of 1,092 individuals in the Ghund area of the State, seven males and an equal number of females were found to be suffering from donovanosis Information on the prevalence of the disease in the other States of the vast subcontinent is sadly lacking, but it is the authors' impression that cases are missed, incorrectly diagnosed, or described under a wrong name in the other areas of the country where, probably, the incidence is low A greater awareness of the disease on the part of the physician and a routine examination of smears from suspected lesions will help to uncover more patients suffering from the disease in the various Indian States

Racial

The overwhelming predominance of the disease in the Negroes of the USA (Negroes, 88%, ' whites ", 12%) and the Dravidians of southern India seems to point to some racial susceptibility Its occurrence among the " poor whites " of the USA, the Paharis of the Simla Hills (though to a diminished extent), and other coloured peoples of the tropics, would, however, suggest that low socio-economic status, with its concomitant evils

of ignorance, lack of personal and sexual hygiene, and debased sexual standards, may account for the differences in racial incidence The same environmental factors account for the greatly increased incidence of syphilis and other venereal diseases It is stated that the stratum corneum of the genito-inguinal region is thinnest among the coloured races, and the apocrine glands more abundantly distributed Is it possible that these two factors in the composition of the skin account for the greater predisposition *of the coloured races ?*

American writers [27] are fond of quoting the figures furnished by Nair & Pandalai and Menon on the much greater incidence of the disease among the Hindus than among the Mohammedans of India (the ratios respectively being 70 1 and 57 4) in support of the theory of racial susceptibility In the first place, however, the figures they report are from Madras State only, where the disease is endemic, and do not apply to India as a whole Secondly, the Hindus and Mohammedans of southern India belong to the same racial stock, distinguished only by their religion Thirdly, the Hindus constitute 92% of the population of the State Fourthly, the Mohammedans practise circumcision, and the incidence of diseases such as syphilis and penile cancer is much less common among them Lastly, in both cases donovanosis is almost exclusively a disease of the unhygienic and sexually promiscuous sections of the population

Climatic

Although it is true that the disease is more prevalent in countries with a warm and humid climate, this alone cannot be a determining factor because the Negroes, living in the northern and north-eastern States of North America, which have a temperate climate, and the Paharis, living in the Simla Hills in a similar climate, are equally victims of the disease Europeans living in the hot and humid tropics have rarely suffered from the infection

Age and sex

An analysis of the records of the venereal diseases clinic at the Government General Hospital, Madras, for a 20-year period (1931 51) shows that 1,350 males and 652 females were diagnosed and treated for donovanosis Fox's [24] records also showed a preponderance of males other observers however—Galloway,[25] Manson Bahr,[52] and Nair & Pandalai [57]—reported that the disease is more common in the female sex It may be stated in this connexion that the patients who attended the clinic at Madras were drawn from all over the State and were more representative than those who attended clinics in regional or linguistic areas It was a matter of great difficulty to determine accurately the marital status of the woman Although

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the records, as entered on the case-cards, showed a slight predominance of married women over unmarried, a closer investigation into the so-called marital status reveals many deserted wives, frequently-exchanged mistresses, and widows The marital bond is almost non-existent among certain sections of the population, partners are discarded and new partners are taken, for economic reasons, wives practise clandestine prostitution To sum up, it is our impression that particularly unhygienic sexual promiscuity is the background of patients suffering from donovanosis A ten year break down of 858 patients according to age and sex is shown in table I

TABLE I DISTRIBUTION OF DONOVANOSIS ACCORDING TO AGE GROUP 1932-41

Age group (years)	Male	Female	Total	Percentage
Under 12	3	2	5	—
13-20	77	59	136	16
21-30	292	139	431	70
31-40	123	54	177	
41-50	55	24	79	
51-60	20	4	24	12
Over 61	5	1	6	
Total	575	283	858	

As in the case of other venereal diseases, the incidence of donovanosis is greatest during the period of sexual maturity from 20 to 40 years of age, patients in this age group comprise about 70% of the admissions in the venereal diseases clinic at Madras The next age group in the order of incidence is 13 20, forming 16% of the admissions A few cases in immature persons have been reported In our study there were five such cases—two female and three male, all under 12 years of age, the former with genital granuloma and the latter with peri anal granuloma as a result of pederasty

Other

The clinical incidence of donovanosis, as compared with that of other venereal diseases such as syphilis and gonorrhoea, is negligible, giving rise to about 1 5% of the total admissions for all venereal diseases Many observers have raised the question whether donovanosis is from its inception a clear cut separate disease or a condition superimposed on a pre-existing traumatic or venereal lesion such as chancroids, bubo, etc Many cases of donovanosis are found without other venereal infections Traumata such as circumcision or opening of buboes help only to promote spreading of a pre-existing infection

CHAPTER 3

ETIOLOGY

In 1905, Donovan [21] at Madras described the presence of certain intracellular bodies in the exudate from the oral granuloma of a patient who also suffered from genital lesions According to him they looked like "gigantic bacilli with rounded ends" (see fig 1) Since then a number of workers have confirmed Donovan's findings These micro-organisms are so constantly present in the lesions of the disease that a clinical diagnosis of donovanosis is not complete without their demonstration With the successful reproduction of the disease in human volunteers by Greenblatt and co-workers,[32] and more recently by us in the clinic at Madras by injecting a pure substance of Donovan organisms obtained from an unruptured bubo, or by transplanting subcutaneously a small piece of granulation tissue from an infected one, a step forward has been taken to corroborate Donovan's observation that the organisms he described are the causative agents of the disease

The nature of the Donovan organisms remained until recently a matter of controversy The earliest workers (Donovan [21] Carter,[9] and Symmers & Frost[77]) believed the organism to be a protozoan belonging to the gregarine order of Sporozoa Later workers (Walker,[80] Goldzieher & Peck,[26] DeMonbreun & Goodpasture,[17] and Menon [56]) as the result of their cultural studies classified it as a bacterium Still later, in 1938, Dienst and co-workers [19] of the University of Georgia Medical School attempted to revive the protozoal theory when they failed to grow the organism in various artificial media A study of the literature on the subject up to 1943 leaves us in great doubt as to whether the causal agent of donovanosis had even been cultivated at all A great advance in our knowledge of the disease came in 1943 when Anderson [1] successfully cultivated the Donovan organisms in the yolk and yolk sac of the developing chick embryo Several investigators [21] [22] [23] have since confirmed her findings, and have succeeded in culturing the organism from the primary culture in cell free medium consisting of unmatured yolk to which agar is added So far, however, no success has attended attempts at primary cultivation of the organism in any artificial medium It is surmised that some factor furnished by living cells, whether in human cutaneous tissues or in developing chick embryo, is necessary for the growth of the organism

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From a morphological and cultural point of view it is concluded that the Donovan micro-organism is bacterial and bacillary. It is not pathogenic to any of the laboratory animals. Anderson et al.[3] carried out both complement-fixation tests and skin sensitivity tests with the cultured organisms, and established an immunological relationship to the disease, but the experimental inoculation of the cultured organisms in human volunteers failed to reproduce it. These workers have proposed the creation of a new genus of pathogenic bacteria with the cultivated strain as the type. For the genus they have proposed the name *Donovania*, and for the specific type, the name *Donovania granulomatis*. Rake,[70] from his studies, suggested that *D. granulomatis* may be related to members of the tribe Escherichieae because of the similarity of antigenic pattern between the former and the latter. He put forward the hypothesis that *D. granulomatis* may be faecal in origin, with a strongly developed tissue tropism. On this hypothesis he tried to explain the peculiar epidemiology of the disease which occurs in individuals whose personal hygiene is low, and in regions of the body likely to be constantly contaminated with faecal material.

Packer & Goldberg[60] studied the specificity of *D. granulomatis* antigens against sera from patients with ulcerative lesions of the rectum and genitalia other than donovanosis, and subject to faecal contamination, but failed to observe any non-specific reaction. Further, if the hypothesis of faecal origin of *D. granulomatis* is to be accepted, the most frequent site of the disease should be the rectum and anus rather than the genitals and groin.

Morphology of Organism

The open lesions of donovanosis should be thoroughly and repeatedly cleansed with saline-soaked gauze, followed by gentle wiping with dry gauze. As the Donovan micro organisms are strict parasites of the large mononuclear tissue cells, a fragment of granulation tissue must be obtained for their successful demonstration (see fig. 2). It is waste of time and effort to examine the surface exudate for the parasites, especially in long standing grossly infected lesions. A small piece of the friable granulation tissue may be obtained from the edge of the lesion by means of a curette, forceps, the sharp end of a broken slide, or the edge of a safety razor blade. The tissue is placed between two slides. While one slide is kept stationary, the other is moved in a circular direction at the same time as firm pressure is applied. An evenly spread smear is obtained on both slides.[7] Leishman[a] or Giemsa stain may be used to stain the "spreads", for routine diagnostic use we have found Leishman stain very satisfactory. The dye should be allowed to remain in contact with the smear for one minute and a half

[a] Leishman stain is one of the modifications of Romanowsky stain and is similar to what American workers call Wr ght s stain

before being diluted with distilled water. The diluted stain should be allowed to remain for five minutes. Another simple and satisfactory method of staining for Donovan organisms recently recommended by Greenblatt *et al*[33] is the use of 1% pinacyanole ($C_{25}H_{25}N_2I$) dye with methyl alcohol. The dye is allowed to act for one and a half to two minutes before it is diluted with distilled water. The diluted stain is allowed to remain for a further one-and-a-half to two minutes. The capsulated Donovan bodies stain a purplish pink and the chromatin inclusions a dark blue.

The two characteristic features of the organism observed in tissue smears are (*a*) the extreme pleomorphism, and (*b*) intracellular parasitism in the mononuclear tissue-cells. In cultures of *D. granulomatis* in the yolk of living chick embryos all the morphological variations observed in tissue smears from human lesions occur. The morphology of the organism, based upon the examination of tissue smears from human lesions, is described below.

Examination of a stained tissue smear shows red blood-cells, neutrophil and eosinophile leukocytes, plasma cells, and lymphocytes. The most characteristic feature in the cytological picture, however, is the presence of scattered large mononuclear cells with round, oval, or bean shaped nuclei. The size of the macrophages varies from 20μ to 60μ. The Donovan organisms are found inside these large cells and occur in two forms, the capsulated and the noncapsulated. The capsulated organism is an ovoid or bean shaped body, varying in size from 1μ to 1.5μ in length, and from 0.5μ to 0.7μ in thickness, and consisting of a well-defined dense pinkish material surrounding a blue bacillary body with dark blue or black chromatin inclusions. These minute inclusions in the body of the organism may be rounded or rod shaped, and disposed centrally, peripherally, or in a bipolar fashion. The older capsulated forms take the stain so deeply, assuming an almost homogeneous purplish pink, that the minute inclusions are scarcely recognizable. It is probable that they are the degenerating forms.

The noncapsulated forms occur as minute deeply stained bodies of varying morphology—coccoid, bacillary, diplococcoid—with or without a closed safety-pin appearance, and surrounded by a halo of unstained area. The size of these immature young forms varies from 0.6μ to 1μ.

Both the mature capsulated and the young noncapsulated forms of the organism may occur scattered in thick clusters or in cystlike spaces inside the mononuclear cell, and both the forms may occur in the same cyst. In acute, rapidly spreading lesions the young forms predominate and are found both inside and outside the mononuclear cells. In chronic lesions the capsulated forms prevail and are sometimes found in single or multiple morula like masses inside the mononuclear cells, often overlying and obscuring the nucleus of the cell. Occasionally the organisms are found inside polymorphonuclear leukocytes. When the mononuclear cell is heavily parasitized, the cytoplasm either disappears or has a faintly

vacuolated appearance Besides these organisms, certain inclusion bodies are observed inside the mononuclear cells The most frequently observed type of inclusion is one or more sharply defined globular masses staining homogeneously a deep pink, or less often a deep blue, and lying away from the intact nucleus of the cell A second type of inclusion seen is a mass of deeply staining spherical bodies almost filling the cell and obscuring the nucleus The inclusions do not appear to be of nuclear origin because the nucleus of these cells is intact The Donovan organisms can be demonstrated in 90% 95% of lesions of donovanosis They may be absent, or with difficulty demonstrable, in (1) acute destructive lesions caused by a superimposed fusospirillary infection, (2) the cicatricial or sclerotic type of granuloma, and (3) very early cases It cannot be too strongly emphasized that the demonstration of the organism is often difficult, particularly in very early lesions of less than a week's duration and diligent and protracted search may be necessary, involving the taking of more than one smear It has been our experience that in early lesions the organisms are atypical, few in number, and extracellular, requiring for their identification a trained eye and patient search

Pathology

The disease has a predilection for moist stratified epithelium Through some breach of the surface of the skin or mucous membrane the Donovan organism gains entrance and sets up an inflammatory cellular reaction in the corium and, to a lesser extent, in the subcutaneous tissue The earliest macroscopic lesion is a small raised flat topped nodule, the size of a pea, and covered by skin The epithelium overlying the nodule becomes boggy and macerated and in a few days excoriates In other cases a subcutaneous swelling of varying size is the initial lesion The swelling softens and becomes a small abscess In either case an ulcer is formed by the loss of the over lying skin The ulcer is indolent looking, with a raised soft bright pink velvety vascular base and a crenated or wavy bluish edge The further evolution of the disease process will be dealt with in Chapter 5 (see page 24)

Histology

The histological characteristics of donovanosis have been described by many students of the subject over the past 40 years The chief features are (1) the massiveness of the cellular reaction in the corium, resulting in the growth of an exuberant granulation tissue, and (2) an associated hyperplasia of the marginal epidermis (see fig 3) The real specific diagnostic feature of the disease is the condition of the corium, although there is a

tendency on the part of pathologists to lay special stress on the epithelial changes, which are common to many other chronic inflammations of the integumentary system. Histological examination of an early nodule shows a dense cellular infiltration of the corium, together with desquamation of the superficial layers, and oedema of the deeper layers, of the epidermis. With the increase in the cellular infiltration of the corium at the papillae, the epidermal layers become attenuated and ultimately disappear. The denuded ulcerated area consists of a luxuriant granulation tissue. The type of cellular reaction on the surface of the ulcer is predominantly polymorphonuclear, with a few scattered eosinophile leukocytes, mononuclear and plasma cells, and mast cells.

The outstanding features of the marginal epithelium are (*a*) a remarkable degree of acanthosis, (*b*) irregular elongation of the rete pegs forming an interlacing network enclosing islands of exudate comprising plasma cells, a smaller number of polymorphonuclear leukocytes, eosinophils, monocytes, and occasional lymphocytes (see fig 4), collections of polymorphonuclear leukocytes are also observed in some of the spaces nearer the surface, resembling miliary abscesses (see fig 5), (*c*) pseudo-epitheliomatous hyperplasia may be a prominent feature (see page 37).

The excessive, irregular, epithelial proliferation in some cases is so suggestive of early malignancy that the literature on the subject—even from seasoned pathologists—contains much confusion and doubt. Below the surface, at the papillae and at the spreading edge of the ulcer, the granulation tissue is rich in plasma cells, lymphocytes, and scattered large mononuclear cells (see fig 6). Running through the dense plasma-cell infiltration a network of capillaries can be seen, with marked hyperplasia of the endothelium, often giving the appearance of solid cords of large pale staining cells (see fig 7). Proliferation of fibroblasts is well marked in the deeper layers. In old cases, and in the hypertrophic type of granuloma, an extensive fibrous tissue reaction is observed with collections of plasma cells, lymphocytes, and mononuclear cells here and there in the crevices of the interlacing strands of fibrous tissue (see fig 8). In the sclerotic or cicatricial type of granuloma, thick bundles of a hyalinized collagenous fibrous tissue dominate the histological picture. Giant cells, caseation, and suppuration are conspicuous by their absence from the lesions. At the periphery of the ulcer the cellular infiltration extends for a variable distance into the normal skin, showing that the infection spreads centrifugally from the infected corium. The presence of the large mononuclear cells in sections of donovanosis was first identified by Goldzieher & Peck[34] and was subsequently described in detail by Pund & Greenblatt.[44] The latter workers claimed that the mononuclear cells they described are specific for donovanosis and are as significant as the Sternberg Reid cell is in Hodgkin's disease, they have termed the cell the "pathognomonic cell of granuloma venereum". These cells are scattered in variable numbers

vacuolated appearance Besides these organisms, certain inclusion bodies are observed inside the mononuclear cells The most frequently observed type of inclusion is one or more sharply defined globular masses staining homogeneously a deep pink, or less often a deep blue, and lying away from the intact nucleus of the cell A second type of inclusion seen is a mass of deeply staining spherical bodies almost filling the cell and obscuring the nucleus The inclusions do not appear to be of nuclear origin because the nucleus of these cells is intact The Donovan organisms can be demonstrated in 90%-95% of lesions of donovanosis They may be absent, or with difficulty demonstrable, in (1) acute destructive lesions caused by a superimposed fusospirillary infection, (2) the cicatricial or sclerotic type of granuloma, and (3) very early cases It cannot be too strongly emphasized that the demonstration of the organism is often difficult, particularly in very early lesions of less than a week's duration, and diligent and protracted search may be necessary, involving the taking of more than one smear It has been our experience that in early lesions the organisms are atypical, few in number, and extracellular, requiring for their identification a trained eye and patient search

Pathology

The disease has a predilection for moist stratified epithelium Through some breach of the surface of the skin or mucous membrane the Donovan organism gains entrance and sets up an inflammatory cellular reaction in the corium and, to a lesser extent, in the subcutaneous tissue The earliest macroscopic lesion is a small raised flat topped nodule, the size of a pea, and covered by skin The epithelium overlying the nodule becomes boggy and macerated and in a few days excoriates In other cases a subcutaneous swelling of varying size is the initial lesion The swelling softens and becomes a small abscess In either case an ulcer is formed by the loss of the overlying skin The ulcer is indolent looking, with a raised soft bright pink velvety vascular base and a crenated or wavy bluish edge The further evolution of the disease process will be dealt with in Chapter 5 (see page 24)

Histology

The histological characteristics of donovanosis have been described by many students of the subject over the past 40 years The chief features are (1) the massiveness of the cellular reaction in the corium, resulting in the growth of an exuberant granulation tissue, and (2) an associated hyperplasia of the marginal epidermis (see fig 3) The real specific diagnostic feature of the disease is the condition of the corium, although there is a

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The parasite, and the host and his environment, should be subjected to organized, detailed, and adequate study to find completely satisfactory answers to some of the problems posed above The Donovan organism is a signal example of a parasite which is pathogenic only to man and has its growth and multiplication inside mononuclear cells None of the laboratory animals is susceptible to infection In human beings, clinical observation suggests that individual susceptibility to infection plays a significant role The organism seems to have a low grade of infectivity, and in this the disease resembles leprosy The degree of morphological variation which the micro-organism exhibits, both in human tissues and in cultures in chick embryo, is another notable characteristic Individual host susceptibility, a rigidly restricted parasitism, and the pleomorphism of the organism, may explain the low percentage of disease as compared with syphilis, and the infrequency of infections in the sexual partners It may be that the disease is infectious only during a brief phase of its evolution

Racial differences in the incidence of the disease may be explained by social conditions and sex habits, as has already been pointed out The difference in the sex distribution of the disease, as reported by different workers, seems to vary from clinic to clinic In our study the number of male patients with donovanosis who attended the clinic during a ten year period was more than twice the number of female patients The same male preponderance is observed even in the case of syphilis and gonorrhoea Hence, the hospital figures do not convey an idea of the real extent of prevalence of the disease among the population

The majority view of the sexual transmission of the disease is based on the following grounds

(1) In the vast majority of the male patients with donovanosis a definite history of sexual exposure before the appearance of the ulcer could be elicited For obvious reasons such a history is not obtainable in women

(2) The initial lesion of donovanosis occurs on the external genitalia in 90% of the cases studied The spread of the disease to adjacent regions such as the groin or the cruro scrotal fold is secondary to the genital lesion

(3) The greatest incidence of the disease falls during the age period of maximum sexual activity In our study 86% of patients suffering from the disease were between 15 and 40 years old

(4) The relative incidence of primary peri anal and anal donovanosis in men and women is 4 1, and the quadruple predominance in the male can be attributed only to the practice of pederasty In our study we have verified this to be true of almost all male patients with the anal lesion

(5) The occurrence of extragenital lesions, far from being a point against [illegible] In the analys[illegible]
of our [illegible]
disease [illegible]

genital granuloma, and the fact that the disease is occasionally seen in children or sexually inactive persons, prove nothing.

(6) The disease is more often found in persons who are sexually promiscuous, although cases not associated with promiscuity occasionally occur.

(7) The main argument cited by some clinicians against the venereal origin of the disease is the rarity of infection among partners in sexual relationships. Clarke,[12] in an illuminating discussion on the subject, has quoted eleven cases of partner infections reported in the American literature. During the past three years (1950-3) 30 cases of partner infections among 250 cases of donovanosis were observed at the venereal-diseases clinic at Madras.

The epidemiological investigation of the partner who is not seeking treatment is a matter of great difficulty. The infected person of either sex is often unable or unwilling to bring the partner for examination; in many cases, however, by careful history taking the presence of the disease may be inferred. From the many case histories it would appear that the disease was mild and healed spontaneously, while in the other partner the disease became established. It is also our observation that in conjugal or partner infections the topographical extent of the disease in the male was limited and stationary, although chronologically older by many months, while the disease in the female case was much more extensive, although of more recent origin. For example, an unmarried male had been suffering for over a year from a small, painless, stationary ulcer on the ventro-lateral aspect of the coronal sulcus as a result of sexual exposure with an unknown woman. As the ulcer was small and painless, and did not trouble him, he had not sought medical advice or treatment. He married, and four months after the marriage the young wife developed extensive ulceration of both labia majora with pseudo-elephantiasis of the clitoris. It was at this stage that both reported for treatment at the clinic. It is our considered opinion that partner infections are not so rare as is made out, and that with detailed painstaking epidemiological investigation many more cases will be brought to light.

CHAPTER 5

CLINICAL FEATURES

Appearance of Lesions

The incubation period of donovanosis shows extreme variations, from a few days to as long as four to five months In many patients who present themselves with fully developed lesions, it has been difficult to find out when the disease actually started In the experimentally induced infection in human volunteers, McIntosh,[43] and Greenblatt and co workers[32] have separately reported an incubation period varying from 42 to 50 days for the development of a typical granuloma In our study of a limited series of early disease of less than four months' duration, the incubation period, as elicited from the patient, varied from two weeks to one month In the disease experimentally induced in a human volunteer by the transplantation of tissue from a streptomycin resistant case of granuloma, we found the incubation period to be 17 days

Early or initial lesions

Some writers, including the senior author (R V R) at one time believed that there was a primary lesion in donovanosis comparable with the primary lesion of syphilis or lymphogranuloma venereum Careful observation and study of a large number of patients with early lesions has shown, however, that the early initial lesion does not differ qualitatively from the typical granuloma

Before describing the clinical features of the disease it may be worth while to emphasize two points

(1) The initial and primary site of the disease is genital in the majority of cases The occurrence of the disease in other parts of the body such as the inguinal, peri anal, and oral regions, is secondary to the genital infection in a very large proportion of cases In the past, undue stress has been laid on the inguinal location of the disease Even in patients presenting themselves with inguinal granuloma with no active lesion of the genitalia, there is a history of a genital lesion or depigmented scar of past ulcer in the genitalia in about 75% of cases

(2) The disease has a predilection for moist stratified surface epithelium of the cutaneous, mucocutaneous, and mucous surfaces of the genital, inguinal, anal, and oral regions of the body

The earliest lesion may be a button like papule, a subcutaneous nodule, or an ulcer The papule, a quarter of an inch to half an inch in size, is firm, raised above the surface, flat topped, and covered by skin or mucous membrane In a few days the overlying epithelium excoriates and an ulcer is formed The papule may represent the initial lesion as well as a means of propagation in long standing cases (see fig 10 and 11)

The subcutaneous nodule or swelling seems to be much less common and is frequently mistaken for a bubo when it occurs in the inguinal region The nodule, at first firm and of varying size, slowly softens and becomes an abscess which may burst of its own accord or, more often, is opened by the surgeon A typical granulomatous ulcer is formed in either case Greenblatt and co workers [27] have termed it " pseudo bubo " in contra-distinction to the real bubo or lymphadenitis (see fig 12) In spite of the fairly large number of patients with donovanosis who have been examined and treated at the venereal-diseases clinic in Madras during the past two decades, we have only infrequently encountered this early type of subcutaneous unruptured granuloma (see fig 13)

The ulcer is the commonest early lesion of the disease It varies in size, is soft, velvety, and bright pink in colour, with a wavy or serpiginous outline, it is comparatively painless and is covered with a film of sero sanguineous exudate or a thin translucent parchment like crust (see fig 14)

In the male, the prepuce, frenum and glans penis are the usual sites In the female, the labia minora mons veneris, and fourchet are the common sites (see fig 15, 16, and 17) From the initial lesion the disease spreads slowly along the various moist folds of the genitalia, taking months to involve a fair sized area The disease spreads in various ways

(1) by direct continuity of tissue along the corium of the skin

(2) by auto inoculation of adjacent or opposing surfaces (contact infection),

(3) by mediate transmission through infected clothes or finger nails

Greenblatt and co-workers [27] claim that the disease may spread through the lymphatics, and explain the occurrence of pseudo-bubo in the groin by postulating the spread of infection from a genital lesion via the lymphatics to the regional lymph node and from there to the subcutaneous tissue and corium of the overlying skin It is difficult to conceive of such a lymphatic spread of infection without clinical and pathological involvement of the lymph nodes and the intervening tissues The finding of endothelial hyperplasia and focal collection of mononuclear cells, without the presence of Donovan organism in the regional lymph nodes, appears to be a non specific reaction to the secondary bacterial contamination of the lesions

The absence of involvement of the lymph nodes, even in extensive long standing cases of donovanosis, is one of the diagnostic hall marks of the disease Our histopathological studies of lymph nodes, both in genital

and inguinal granuloma, and in oral lesions, have revealed no histological change in the nodes which might suggest infection by Donovan organisms The presence of palpable or enlarged lymph nodes in association with genital granuloma may be due to one of four coexisting causes

(*a*) superadded secondary infection with non specific organisms ,

(*b*) lymphogranuloma of the lymph nodes,

(*c*) early latent syphilis,

(*d*) malignant metastasis

Table II gives the various *sites of infection in* 858 *patients* who attended the venereal diseases clinic at Madras over a ten year period

TABLE II TOPOGRAPHICAL DISTRIBUTION OF DONOVANOSIS IN 858 PERSONS

Site of infection	Number of male cases	Number of female cases	Total number of cases
External genitalia only	312	160	472
External and Internal genitalia	—	4	4
Internal genitalia only	—	2	2
Genito inguinal	127	22	149
Genito inguino anal	14	10	24
Genito perineo anal	10	68	78
Genito oral	30	9	39
Inguinal only	38	1	39
Inguino anal	3	1	4
Inguino oral	4	—	4
Inguino crural	1	—	1
Peri anal and anal only	28	6	34
Anal oral	2	—	2
Genital-oral cervical	3	—	3
Oral only	2	—	2
Buttock	1	—	1
Total	575	283	858

An analysis of the table reveals

(*1*) The *overwhelming predominance of genital lesions and secondary* spread to neighbouring areas (90%)

(2) The greater tendency of the genital lesion in the male to extend upwards and outwards towards the inguinal regions (see fig 18), as con

trasted with the frequency of genital lesions in the female tending to spread downwards and backwards towards the perineum and peri-anal regions (see fig 19)

(3) Donovanosis confined to the peri anal and anal regions shows a marked preponderance in the male, for the obvious reason that the practice of pederasty is almost invariably confined to males

(4) Extragenital lesions are almost exclusively confined to the oral lesions in our series and are invariably secondary to long-standing genital granuloma Only two patients with primary oral granuloma were encountered in the study An extension of the disease to the skin of the cervical region from lesions in the mouth was observed in a dozen cases (see fig 20 and 21)

(5) The occurrence of the disease in the deeper parts of the vagina and cervix was observed in 18 cases, either in association with vulval lesions, or as primary solitary lesions It is our impression that primary donovanosis in the inguinal region, as well as extension of the infection to the neighbouring areas, was observed in 5% of the patients

The evolution of the disease, as has already been stated, is very slow In the male, from the initial lesion on the prepuce or glans penis the infection may extend to the stem of the penis, encircle the root, involve the penoscrotal junction, and spread upwards and outwards along the inguinal regions or downwards and laterally along the cruro-scrotal folds or round the root of the scrotum

In the female, the ulcer starting in the labia minora may spread laterally to the labium majus, and upwards to involve the crura of the clitoris and the mons veneris, or downwards to the fourchet, perineum, and peri anal region In long standing cases the disease may extend inwards to the vaginal introitus, the vagina, and the cervix

The disease has not been known to affect the rectum or the urethra, although some writers have loosely described the extension of the disease to these parts It is true that the stratified epithelium of the urethral orifice and the anus are frequently infected by an extension of the disease from the glans penis of the male and the vestibule of the female in the former, and from the peri anal region of both sexes in the latter However, the columnar epithelium lining the urethra and the rectum seems to be resistant to invasion by the organisms of donovanosis The extension of the disease to the uterus, tubes, and ovaries is exceedingly rare, although Pund & Gotcher[43] reported a case in 1938

Extragenital lesions

Next to the involvement of the genitalia and their environs, the oropharyngeal cavity is most frequently the site of the disease Extragenital granuloma has been reported by a number of workers, but it would seem

and 29) Its cause is mechanical, being pressure of scar tissue on the lymphatics, and it is not dependent on the duration or chronicity of the disease Particularly in women, early localized lesions of a few months' duration tend to cause elephantiasis of the vulva and clitoris

Stenosis of the urethral, vaginal, and anal orifices may result from the sclerotic type of donovanosis, and cause difficulty in micturition, defaeca tion, and parturition In the process of healing of extensive vulva lesions, the lips may become adherent along the entire extent, causing occlusion of the vaginal introitus and resulting in a sort of pathological infibulation (see fig 30)

Various deformities follow long standing ulceration in the various regions Adhesions of the penis to the scrotum, incarceration of the organ into the skin of the scrotum, partial or total amputation of the penis (see fig 31) lateral and backward deformity of the phallus, are the chief, obvious sequelae of venereal granuloma in the male In the female the normal anatomical architecture of the external genitalia may be destroyed by ulceration and scar tissue In oral donovanosis, adhesions of the lip and cheek to the gums cause microstomia and difficulty in opening the mouth Difficulty in swallowing and regurgitation of food through the nose, occur, seriously inconveniencing the patient

A depigmented scar is left when the ulcer heals The scar may be soft and supple or hard and unyielding In the course of time the white scar gradually becomes pigmented in patches Epidermoid carcinoma may occur as a complication of, or a sequel to, long standing donovanosis, but the complication seems very infrequent as only 0 25% in 2,000 cases were discovered with cancer

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reveals an abundance of bacterial flora, the fusospirillary group of organisms being the most numerous, but Donovan *organisms disappear from the* surface exudate The inflammation rapidly spreads both superficially and deeply, destroying the tissues in its wake In the female, the vulva, perineum, and *peri anal region may be completely destroyed, and the recto-vaginal* septum represented by a gaping cloacal pus filled cavity In the male, necrosis of the genitalia, particularly of the penis, may occur and partial or complete amputation of the organ is a not uncommon result of virulent fusospirillosis The patient with a severe infection has fever, displays toxic symptoms, and suffers from an acute secondary anaemia The condition occasionally proves fatal (see fig 27)

Course and Termination

The disease is chronic and its course is slow in our study its duration, from the time when the patient presented himself for treatment, varied from a fortnight to 35 years, the most usual period being about two and a half years The tendency to recurrence of ulceration in apparently healed cases is great The general health remains unaffected for a long time Some patients complain of pain over the ulceration, others, especially women, suffer from intolerable itching of the genitalia In many patients, the disease is so advanced that sexual function is difficult or impossible Others with earlier lesions are able to lead a normal sex life for some time Infected women may become pregnant and give birth to healthy children *who do not suffer from the disease, but very often the pregnancy ends in* miscarriage or abortion The disease may cause mechanical difficulty in micturition, defaecation, sexual intercourse, and parturition, and in *extensive disease of the genito-inguino-anal regions in walking as well* The plight of patients with advanced granuloma is very distressing the disease in its late stages is as incurable as advanced cancer or leprosy They seek *relief at different hospitals, are deserted by their partners and relatives,* become derelicts of society, and often commit suicide in despair

Patients rarely die of the disease itself Progressive secondary anaemia, a fulminating *septic infection, tuberculosis of the lungs and intestines, and,* in a few cases, the development of epidermoid carcinoma, may be the *terminal causes of death Eight fatalities occurred among the patients in* the series under review, in five of whom tuberculosis of the lungs was the cause of death Two died suddenly after an injection of an antimonial compound The eighth patient died of a fulminating fusospirillary infection

Complications and Sequelae

Pseudo-elephantiasis of the genitalia occurs in *15% 20% of patients* with donovanosis, and is more common in women than in men (see fig 28

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CHAPTER 6

DIAGNOSIS

Methods

It should be constantly borne in mind by the medical practitioner in the tropics that mere dependance upon clinical methods of diagnosis of ano-genital lesions is frequently unreliable and may trip even the trained, seasoned specialist into a wrong diagnosis It is not uncommon to find the association of two or more disease entities in the same individual, with a consequent change in the clinical picture Our studies show that donovanosis is associated with chancroids, syphilis, or lymphogranuloma venereum either alone or in combination, in about 10% 20% of the cases On rare occasions, penile cancer and donovanosis, and cutaneous amoebiasis and donovanosis, are encountered in the same patient Accurate diagnosis of ano genital lesion requires the performance of a battery of laboratory tests It has been our routine practice to subject every ulcerating ano genital lesion to the following tests

(*a*) expressed serum for darkfield examination of *Treponema pallidum*,

(*b*) smear stained with Gram stain for the streptobacillus of Ducrey,

(*c*) tissue smear stained with Leishman stain for *D granulomatis*

Clinically, the occurrence of an indolent soft granulomatous ulcer with a homogeneous velvety bright pink base and a wavy edge, in the genital, inguinal, or peri anal regions, with a history of antecedent sexual exposure, should be looked upon with suspicion as a probable case of donovanosis The suspicion is strengthened if the ulcer shows no tendency to heal, and is not associated with enlargement of the regional lymph nodes

Tissue smear

The diagnosis should be based on the finding of *D granulomatis* in tissue smears taken from the lesion The morphological and tinctorial characteristics of the organism are so typical that it is easily demonstrable in tissue smears in the large majority of cases, provided the technique described elsewhere (see pages 16 17) is carefully followed In the necrotic grossly infected lesion *D granulomatis* is not easily revealed In such cases a preliminary injection of 600 000 units of penicillin will rapidly clear the

les on of the contaminants, and Donovan organisms can be successfully demonstrated in tissue smears In the long standing, partially healed, cicatricial type of lesion, it may be necessary to perform a biopsy and obtain smears from the cut surface of the specimen for finding the organisms The diagnosis of an early lesion of donovanosis, of one or two weeks' duration is often missed by the general practitioner and even by trained specialists in venereal diseases clinics The reasons for this state of affairs are many There may be a certain lack of awareness of the disease on the part of the physician when it occurs as a small ulcer in the external genitalia, a physician encountering a genital lesion often thinks in terms of syphilis and chancroids and tries the hit or miss therapy of sulfonamides followed by penicillin The still persisting name of "granuloma inguinale" for the disease has emphasized the inguinal regions as the primary anatomical sites and is responsible for the low threshold of suspicion among clinicians when a genital sore is encountered Hence, no attempt is made to examine tissue smears for Donovan organisms, which in very early lesions are scarce, atypical, and extracellular Prolonged diligent search, with repeat smears if necessary, must be carried out before the organism can be identified

Biopsy

Histological examination of biopsy obtained from the lesion is recommended by the workers of the University of Georgia School of Medicine [45] as an additional and more reliable method in the diagnosis of donovanosis

It has been our experience, as it is of other workers, that the organisms are not easily identified in sections prepared with haematoxylin and eosin Pund & Greenblatt [44] recommended the use of Delafield's haematoxylin and eosin or Dieterle's silver impregnation method for a satisfactory and unfailing recognition of the intracellular inclusions

In the routine day to-day work of a busy venereal-diseases clinic, the examination of a properly obtained tissue smear stained with Leishman stain is simple, rapid, and reliable in the diagnosis of a suspect lesion, and any physician with a microscope and a bottle of Leishman stain will be able to perform the test. We do not recommend as a routine procedure on which to base the diagnosis of donovanosis the time-consuming histological examination of sections obtained from the lesion The section method is, however, indicated in two cases (1) when repeated examination of tissue smears in a clinically suspect lesion is negative to *D granulomatis*, and/or (2) when there is a strong suspicion of malignancy in the clinical appearance of the lesion

Immunological Tests

Complement fixation test

Anderson [1] and Anderson, Goodpasture & DeMonbreun,[3] followed by Dunham & Rake,[22] and Dulaney, Guo & Packer,[22] have successfully

established a specific immunological relationship of *D granulomatis* to donovanosis by demonstrating that the sera of patients with donovanosis contain complement fixing antibodies against *D granulomatis* The complement fixation test is claimed as an additional tool in the diagnosis of the disease

Skin test

Kornblith,[45] using an antigen prepared from the superficial tissue of a lesion of donovanosis, tested proved cases of the disease with a series of controls and reported positive intracutaneous reaction in all but two of the cases of donovanosis Anderson and her associates,[3] with the antigen prepared from the embryonic yolk culture, reported positive reactions in all the cases tested Likewise, Chen et al,[10] and Packer & Dulaney[69] have reported similar results A critical study of the several publications on the value of immunological tests (both serological and cutaneous) reveals the following facts

(1) Both the complement fixation and skin tests have satisfactorily established the immunological relationship of *D granulomatis* to donovanosis

(2) The tests seem to be much more subject to limitations of sensitivity and specificity than similar tests for syphilis and lymphogranuloma venereum

(3) The demonstration of *D granulomatis* in tissue smears from active lesions has the highest and most reliable, direct, and specific diagnostic value Hence, the employment of the immunological tests in laboratory proved cases of donovanosis seems superfluous, and wasteful of time and labour

(4) The value of the immunological tests has not been proved in the asymptomatic sexual partners of patients with overt disease and positive tissue smear Hence it is very doubtful whether the tests will help to unravel some of the unsolved problems in the epidemiology of donovanosis

(5) The existence of latent asymptomatic syphilis and lymphogranuloma venereum has been established by both serological tests and epidemiological investigation, whereas donovanosis, as far as present knowledge goes, does not exist in a latent form, and a positive complement fixation test has never been observed in sexual contacts showing no clinical evidence of the disease

(6) A negative complement fixation or skin test may help to rule out donovanosis in patients suffering from chronic ano genital ulceration who are repeatedly negative to *D granulomatis*

(7) The immunological tests will be useful in studying the antigenic behaviour of different strains of the Donovan organisms, and the similarity of antigenic pattern between *D granulomatis* and other allied organisms

(8) It would seem that the sensitivity of the complement fixation test in early lesions of donovanosis is inadequate for diagnostic purposes. The skin test lacks the clear-cut pattern observed with a similar test in lymphogranuloma venereum, and gives false positive reactions in many chronic infections other than donovanosis.

(9) Information is lacking as to whether a change in the titre of the complement fixation test after treatment with streptomycin or antimony occurs in the sera of patients with donovanosis.

Differential Diagnosis

Syphilis

Primary syphilis. The primary sore is easily distinguished by its induration, absence of bleeding, built up base, shelving edge with a red areola, the associated indiarubbery painless enlargement of the regional lymph glands, and the presence of *T. pallida* in the serum expressed from the lesion.

Secondary syphilis. The hypertrophic moist button like papules occurring in the genitalia may have a superficial resemblance to the button-like papule or nodule of early donovanosis. The moist papule of syphilis, however, has a greyish white colour and even when it is eroded it lacks the bright pink easily bleeding characteristic of donovanosis. The history of a primary sore, the occurrence of the secondary lesions in other parts of the body, and the finding of *T. pallida* in the scrapings from the moist lesions help in the diagnosis.

Tertiary syphilis. A gummatous ulcer has a punched-out appearance, with clean-cut vertical edges and a slough-covered base. Nodulocutaneous ulcerating syphilides have the same appearance, with a tendency to central healing and peripheral spread in an arciform, gyrate, or serpiginous fashion. Other evidences of syphilis will be found. A positive serological reaction, and response of syphilitic lesions to antisyphilitic drugs, are other points in the differential diagnosis.

Chancroid or soft sore

A short incubation period of two or three days, the acuteness of the lesion, its multiplicity, the painful angry looking pus-covered ulcer with irregular "mouse-eaten" undermined edge, the acute painful lymphadenitis with a tendency to suppuration, a positive Ito-Reenstierna test, and the presence of Ducrey's streptobacilli in deep scrapings from the lesions, help to distinguish chancroid from donovanosis.

Lymphogranuloma venereum

Although this disease is quite distinct from donovanosis, the two conditions are so frequently confused that it is proposed to list the points of distinction in a tabular form.

Donovanosis (granuloma venereum)	*Lymphogranuloma venereum*
(1) The disease has a predilection for moist stratified epithelium of the genital and oral regions of the body	The disease affects primarily the lymphatic tissue of the inguinal genital, and rectal regions of the body
(2) It is generally accepted that Donovan organisms are the causal agents of the disease, they are easily demonstrated in the exudate or scrapings from the ulcer	Caused by a filterable virus, bacteriological demonstration of the organisms is difficult but can be achieved by animal transmission
(3) *There is no primary lesion distinct* from the typical granulomatous ulcer	*The primary inoculatory sore is usually* a small superficial evanescent herpetiform lesion—it precedes the other manifestations
(4) Constitutional manifestations are absent neither preceding nor accompanying the disease	Constitutional symptoms such as fever, malaise, or arthralgia invariably precede or accompany the onset of the local manifestation of the disease
(5) The typical lesion is an indolent granulomatous ulcer, very slowly spreading and involving the skin of the genital, inguinal and anal regions	The manifestations vary in the sexes, inguinal adenitis with tendency to suppuration and formation of multiple fistulae in the male, hyperplastic and ulcerative changes of the genito-ano-rectal regions in the female
(6) Pseudo-elephantiasis of the genitalia occurs secondary to the ulceration, the ulcer is granulomatous pink, and velvety	Pseudo-elephantiasis of the genitalia, particularly in the female is more frequent and is caused by a virus lymphangitis and lymphostasis The ulceration of the genitalia is secondary to the elephantiasis The ulceration is superficial with irregular serrated edge and a yellowish anaemic-looking base devoid of the raised pink granulations seen in donovanosis
(7) Inflammatory stricture of the rectum is unknown in donovanosis The ulceration stops short of the anus and anal stricture is common.	Inflammatory stricture of the rectum with polyposis and ulceration of the mucous membrane is common and typical of lymphogranuloma venereum.
(8) Donovan organisms can be demonstrated from the ulcers of donovanosis	Donovan organisms are absent in ulceration due to lymphogranuloma.
(9) Frei s intradermal test is negative	*Frei s intradermal test is positive.*
(10) The disease is sparsely distributed, even in endemic areas There is a marked individual susceptibility	The disease is widely prevalent all over the world All races are susceptible
(11) No changes in blood chemistry, hypoproteinaemia in chronic donovanosis in some cases	Hyperproteinaemia with reversal of albumin globulin ratio is a *characteristic feature* of the disease.
(12) Serum fixes complement in the *presence of antigen prepared from D granulomatis*	Serum fixes complement in the presence *of antigen prepared from* cultured virus of the disease.

Epithelioma

When studying the literature, largely American, on the relationship of donovanosis to epithelioma, the authors have noted the frequency with which the former is mistaken for the latter and, less frequently, the latter for the former

Beerman & Sonck,[5] in a paper read before the Tenth International Congress of Dermatology, London, 21 26 July 1952, on the epithelial changes in granuloma inguinale, have posed three questions on the subject and have tried to answer them by both a review of the existing literature and the histological examination of a series of cases of granuloma with a case report

(1) Does granuloma simulate cancer ?

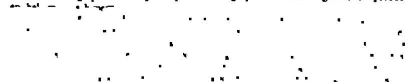
(2) Does cancer develop as a complication on a pre-existing granuloma ?

(3) Do cancer and granuloma occur independently in the same patient at the same site ?

Our own views on this aspect of the disease have been stated elsewhere [68] but we feel it desirable to outline them once more in this paper

"A study of the literature and our experience suggest that the resemblance between the two lesions may be close both on clinical and histological grounds. Granuloma venereum has been mistaken for cancer more frequently than cancer for granuloma venereum The threshold of suspicion for granuloma venereum on the part of the average surgeon and gynaecologist is rather low even in endemic areas and it is not uncommon for mutilating operations [to be] performed on patients in the mistaken diagnosis of the lesion for cancer Kern s [44] report of three cases where squamous-cell carcinoma simulated granuloma venereum even in the presence of Donovan organisms in two of the cases is an example of the reverse mistake in diagnosis The clinical appearance of a chronic long standing granuloma venereum may closely mimic that of an epidermoid carcinoma in the exuberant fleshy growth or in an ulcer with nodular base and everted edge

"In common with other chronic granulomas of the integumentary system such as syphilis tuberculosis, yaws mycotic infection etc., a pseudo-epitheliomatous hyper plasia of the marginal epithelium is a characteristic histological feature of granuloma venereum Fig [32 and 33] are photo-micrographs of various grades of pseudo-



cells with or without the Donovan organisms The predominance of polymorpho-nuclear leukocytes in the superficial part of the ulceration along with the invasion of the prickle cell layer by the same leukocytes is another feature of granuloma venereum which is not usually the case in squamous-cell epithelioma

"In some cases of granuloma venereum of long standing, there may be an extreme hyperplasia and proliferation of the epidermis in an irregular manner with narrow strands

of prickle cells reaching deep into the cutis, with even pearl formation, histologically resembling Grade I squamous-cell epithelioma and the final diagnosis depends on the clinical outcome to antibiotic therapy. With a multiplicity of effective therapeutic agents, such as streptomycin, aureomycin, etc, failure to achieve cure must cast serious *doubt on the validity of diagnosis of granuloma* venereum

" On the second and third questions whether epidermoid carcinoma occurs as a complication of or sequel to granuloma venereum and whether the two conditions may occur independently in the same patient, opinions are not unanimous

" The incidence of epithelioma arising from other conditions which include syphilitic, tuberculous and varicose ulcers, ano-rectal lymphogranuloma, scar of burns and certain precancerous dermatoses, varies from a fraction of 1% to a maximum of 6% according to Orsmby & Montgomery [68] It is likewise conceivable that carcinoma may supervene on a lesion of long standing granuloma venereum for the same reason that it occurs in other chronic cutaneous granulomatous conditions It is also pertinent to point out that both granuloma venereum and epithelioma of the external genitalia, particularly [illegible]

is about 88% among Negroes and 12% among the " poor Whites " of America [USA] [illegible]

endemic reservoir for granuloma venereum

" The study of the titles of the case reports that have appeared in the American literature, such as " Granuloma inguinale simulating carcinoma ", [8] " Granuloma inguinale ? carcinoma ", [74] " Granuloma inguinale clinically diagnosed as carcinoma ", [75] " Carcinoma simulating granuloma inguinale ", [44] reveals the difficulty, doubt and the mistakes that have occurred in the differential diagnosis of the two conditions Chen, [illegible] reported [that] [illegible]

the rigid criteria of correct diagnosis of an earlier granuloma, a response to [illegible] and subsequent development of cancer verified clinically and histologically We consider that a true epitheliomatous change may occur as a late complication of or sequel to long-standing granuloma venereum, but this seems an infrequent occurrence

" The association of cancer and granuloma venereum occurring in the same patient has been recognized by us as affecting the penis in the male and cervix in the female The occurrence in our opinion seems to be merely sequential without any implication of causality In some of the reported cases and also in two patients in our study . . . it would seem that cancer was the earlier lesion chronologically and that granuloma [illegible]

Filariasis

Elephantiasis of the genitalia is a common sequel of filariasis in the tropics, and the pseudo-elephantiasis occuring in donovanosis may be mistaken for the former In filariasis there is no ulceration , the history of frequent attacks of fever and swelling and the presence of microfilaria in the blood help in the diagnosis

Tuberculous ulceration

This is rare in the genito inguinal region and has no resemblance to donovanosis Biopsy shows caseation giant cells, and tubercle bacilli

Cutaneous amoebiasis (ano-genital)

In tropical practice amoebic ulceration of the ano genital region is not uncommon, it bears a superficial resemblance to donovanosis and may be a superimposed infection on a pre-existing lesion of this disease Examination of the unstained exudate from the lesion will reveal active vegetative forms of *Endamoeba histolytica*

CHAPTER 7

TREATMENT

Antimony Compounds

The antimonial compounds such as tartar emetic, urea stibamine (sodium amino phenyl stibinate), Fuadin (sodium antimony III biscatechol 2,4 disulfonate), Anthiomaline (lithium antimony thiomalate), Duramin, and Fantorin, have been used with varying degrees of success in the treatment of donovanosis during a period of nearly 35 years from 1913 to 1947 The success of treatment with antimonial compounds is in inverse proportion to the duration and extent of the disease, the tendency to recurrences after treatment and apparent healing is a marked feature of the disease Such recurrent lesions develop an insusceptibility to further antimonial therapy—antimony fastness Toxic intolerance to repeated therapy with antimony is another serious drawback, and a few sudden deaths have occurred during treatment with the drug Further, it is our impression that antimony is an activator of latent tuberculous infection, the patients in our series who died ultimately of galloping tuberculosis had received interrupted therapy with antimony over a period of years

Antibiotics

In the pre antibiotic era, the sulfonamides were tried without success The initial hope that penicillin, the first of the antibiotics, might prove effective in donovanosis was not fulfilled, although it has a place in clearing up the secondary contaminants in lesions of the disease It was only logical that the other antibiotics, as they were discovered and became available for therapeutic evaluation, should be tried

Barton and his associates [4] in the USA were the first to report, in 1947, on the therapeutic effects of streptomycin on donovanosis Since then a number of additional reports have appeared in American medical literature [31, 42, 43, 78] Greenblatt and co workers [31] have made a detailed study on the largest group of cases (142 patients) treated in that country and, as a result of their experience of treatment with varying schedules, have recommended 4 g of streptomycin daily in divided doses at four-hour intervals for a period of five days An example of response of extra-

genital granuloma inguinale to antibiotic therapy is illustrated in fig 34 About 10% of the patients relapsed and all but four of these responded to a second course of therapy We should like to record our experience with streptomycin in the largest number of cases of donovanosis ever treated in one clinic during a period of three years [66, 69]

227 patients—146 males and 81 females—were treated with streptomycin from August 1948 to September 1951 All the patients were hospitalized and the diagnosis was established by the demonstration of typical intracellular Donovan bodies in tissue smears obtained from the lesions Both streptomycin and dihydrostreptomycin were used in the treatment according to the availability of the drug and no appreciable difference between them was discovered, in either therapeutic effect or toxicity The total dosage of the drug employed varied from 5 g to 70 g, but the largest number of patients received 20 g The individual dose varied from 1 g to 2 g per day, and the duration of treatment extended from 5 to 20 days Best therapeutic results were obtained with 10-20 g of streptomycin administered over a minimum period of 10 days The immediate results were excellent (see fig 35) All but four cases had healed satisfactorily at the time of discharge from the hospital Three of the four refractory cases were treated with either aureomycin or chloramphenicol The fourth streptomycin resistant patient suffered from a concomitant tuberculous infection of the lungs and ultimately died of it in spite of the administration of 70 g of streptomycin Necropsy revealed an advanced disease of the lungs with teeming tubercle bacilli in the tissues This is an example of streptomycin resistance of two chronic infections in the same patient

Toxic reaction

208 of the 227 patients in our series did not exhibit any toxic reaction to the drug Among the remaining 19, vestibular dysfunction occurred in 4, urticaria in 4, headache in 3, fever in 3, conjunctival haemorrhage in 2, dysphagia in 1, diarrhoea in 1, and pain in the abdomen in 1 The reactions were all temporary and did not necessitate discontinuance of treatment. The Donovan organism, the causative agent of donovanosis, is a fastidious tissue-parasite revealing marked pleomorphism This being the case, the organism may be expected to develop an increasing resistance to streptomycin on the analogous experience with antimony in the treatment of the disease In vitro experiments seem to indicate that microorganisms in general develop resistance to streptomycin much more easily and quickly than to other antibiotics

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The latest additions to our therapeutic armament in the treatment of donovanosis are aureomycin, chloramphenicol, and oxytetracycline A number of favourable reports on the subject have been appearing in American medical literature [29, 30, 35-38, 40, 41, 72, 73, 82] Fig 37 and 38 illustrate the effect of chloramphenicol on a case of granuloma inguinale of the cervix On account of their high cost, a large-scale trial of the antibiotics was not practicable in our laboratory In a small series of 32 cases, 19 were treated with chloramphenicol and 13 with aureomycin 17 of the former and 9 of the latter series were cured Recently, 3 cases of streptomycin resistant donovanosis were cured by oral administration of oxytetracycline The initial failures from one drug were cured by a change to one or other of the untried antibiotics

The optimum total dosage is 20 g of the antibiotic administered orally at the rate of 500 mg every six hours Donovan organisms disappeared from the lesion in 3 15 days, and the time taken for the lesions to heal varied from 14 to 40 days, depending upon the extent and duration of the disease No untoward reactions are reported except nausea and vomiting, occurring with orally administered aureomycin Parenteral administration of the antibiotics is very painful, has no advantage over the oral therapy, and is not recommended

Resistance and recurrence

A statistically insignificant number of cases of donovanosis are chemoresistant to initial therapy, irrespective of the type of antibiotic used In other cases, the lesions heal satisfactorily during the period of observation in the hospital, only to relapse and break down after a period ranging from a few months to two years Such recurrent lesions become resistant to the drug which resulted in the initial healing, however, the physician now has at his disposal a multiplicity of specific drugs with which treatment resistance can be circumvented, by the combination of two or more drugs administered simultaneously or successively The well known tendency of the disease to relapse after initial healing should be kept in mind, and a long post treatment observation of about two years is essential to assess the permanence of the initial cure

General Measures

In the majority of cases hospitalization is necessary to ensure satisfactory response to specific therapy The general health must be main-

tained and improved by nutritious food, vitamins, etc Concurrent venereal infections, either recent or latent, should receive attention Secondary infection should be treated by penicillin, and surgical cleanliness should be maintained before specific treatment is started Minor surgical measures, such as excision of elephantoid masses and occlusive deforming scars, and skin grafting, may be necessary in healed cases with deformity and distortion

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CONCLUSION

It is true that the hospital incidence of donovanosis is negligible in comparison with that of syphilis or gonorrhoea in southern India, and the disease is not a major public health problem It is, however, a signal example of the close interrelation between poverty and disease As Winslow[81] has so admirably put it, a man becomes sick because he is poor—he becomes poorer because he is sicker, and sicker because he is poorer This aphorism is particularly true in the case of patients suffering from donovanosis The disease[28] is a terrible affliction which slowly and inexorably ravages its victim Poorly understood, and poorly handled, it becomes so loathsome that the patient is shunned like a leper, there are sanatoria for the tuberculous, and leprosaria for lepers, but the patient with donovanosis goes from hospital to hospital for admission

Few general practitioners are interested in the disease Its victims, as has already been pointed out, come from the poverty stricken, under privileged sections of the population, with poor personal hygiene and debased sexual standards Thanks to the low infectivity of the organism, the disease is prevalent only in a small percentage

In view of the limited nature of the incidence of donovanosis, it should be possible to control and eradicate the reservoirs of infection by an organized public-health drive Early diagnosis and adequate therapy with the antibiotics are the answers to the problem of control

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69 Rajam, R. [illegible]
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ILLUSTRATIONS

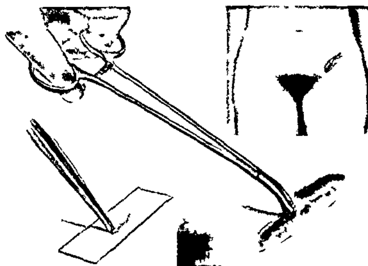
FIG 1 DONOVAN BODIES



Magnification × 970

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FIG 2 TECHNIQUE FOR OBTAINING SMEARS FOR DONOVAN BODIES



* As establ shed at the Med cal College of Georgia Augusta, Georgia, USA

B ur sy of D R B Greenbla Medical College of Georgia USA

FIG 3 HYPERPLASIA OF MARGINAL EPITHELIUM WITH MASSIVE CELLULAR REACTION IN CORIUM



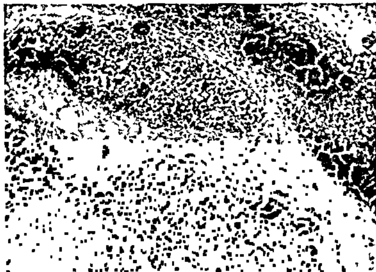
Magnification × 320

FIG 4 ACANTHOSIS WITH IRREGULAR ELONGATION OF RETE PEGS FORMING AN INTERLACING NETWORK ENCLOSING ISLANDS OF CELLULAR EXUDATES



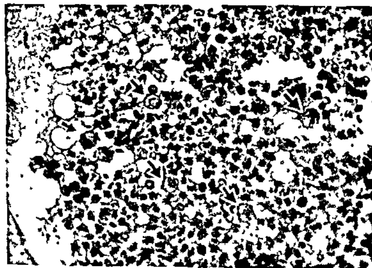
Magnification × 320

FIG 5 HISTOLOGICAL SECTION, SHOWING INTRADERMAL ABSCESSES



Magnification × 160

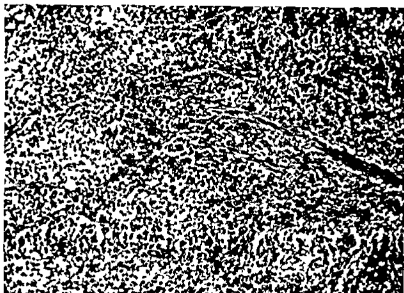
FIG 6 GRANULATION TISSUE SHOWING PLASMA CELLS, LYMPHOCYTES, AND SCATTERED LARGE MONONUCLEAR CELLS *



* Mononuclear cells containing Donovan organisms in cytoplasm indicated by arrows

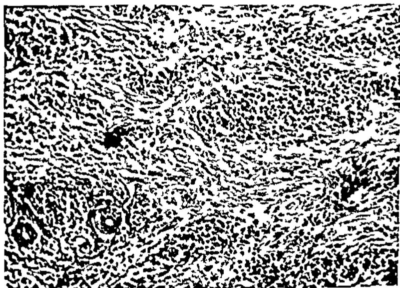
Magnification × 640

FIG. 7. GRANULATION TISSUE WITH MARKED HYPERPLASIA OF ENDOTHELIAL CELLS OF THE CAPILLARIES



Magnification ×320

FIG 8 EXTENSIVE FIBROUS TISSUE REACTION WITH COLLECTIONS OF CELLS IN CREVICES OF INTERLACING STRANDS OF FIBROUS TISSUE



Magnification ×320

FIG 9 HISTOLOGICAL SECTION OF GRANULOMA INGUINALE SHOWING PATHOGNOMONIC CELL* STAINED WITH DELAFIELD S HAEMATOXYLIN

Magnification 1 440

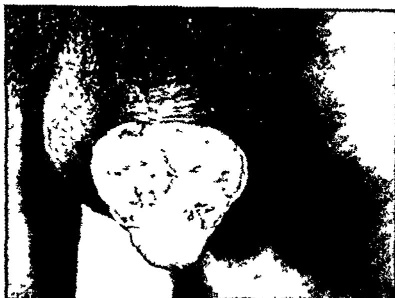
* Indicated by arrow

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FIG 10 EARLY GRANULOMA INGUINALE WITH DAUGHTER LESIONS OFTEN MISTAKEN FOR CONDYLOMA LATA

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FIG 11 MULTIPLE UNBROKEN BUTTON LIKE NODULES ON GLANS PENIS AND INNER LINING OF RETRACTED PREPUCE



Positive for Donovan organisms, duration one month

FIG 12 GRANULOMA INGUINALE OF LABIA



Duration several months with recently enlarging and fluctuating area in left inguinal region (pseudo bubo) on aspiration Donovan organisms found to the exclusion of other organisms

By courtesy of Dr R B Greenblatt Medical College of Georgia USA

FIG 13 PSEUDO BUBO IN GROIN



Aspi ated mate ial positive fo Donovan organisms

FIG 14 EARLY GRANULOMATOUS ULCER ON LEFT SIDE OF PREPUCE



Positive for Donovan organisms , duration 15 days

FIG 15 EARLY GRANULOMATOUS LESION AT FRENULUM



FIG 16 EXTENSIVE ULCERATION ON DORSAL ASPECT OF PREPUCE AND GLANS PENIS



F G 17 ULCERATION OF LABIA MINORA FOURCHET AND CLITORIS



FIG 18 EXTENSIVE GRANULOMA OF PREPUCE AND GLANS PENIS EXTENDING UPWARDS TO BOTH GROINS

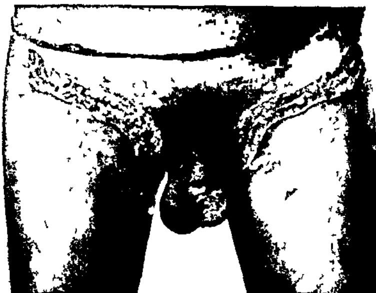


FIG 19 TENDENCY OF ULCERATION IN FEMALE TO SPREAD DOWNWARDS AND BACKWARDS TOWARDS PERINEUM AND PERI ANAL REGIONS



FIG 20 GRANULOMA OF INNER SIDE OF LIPS AND CHEEK SECONDARY TO GENITAL DISEASE



FIG 21 FLESHY TYPE OF GRANULOMA OF NECK SECONDARY TO GENITAL AND BUCCAL GRANULOMA

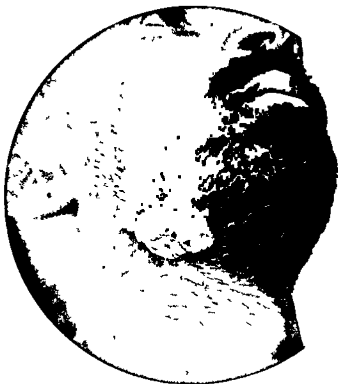
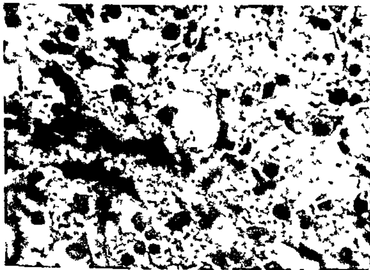


FIG 22 HISTOLOGICAL SECTION OF LIVER BIOPSY SHOWING LIVER PARENCHYMA CELLS CONTAINING DONOVAN ORGANISMS IN VARYING NUMBERS DIETERLE STAIN



Magnification ×720

FIG 23 HISTOLOGICAL SECTION OF LIVER BIOPSY SHOWING CAPSULATED ORGANISMS IN THE LIVER PARENCHYMA CELLS GIEMSA STAIN



Magnification ×720

FIG 24 HYPERTROPHIC TYPE OF GRANULOMA INVOLVING PREPUCE, RIGHT GROIN, AND UPPER PART OF THIGH IN MALE



FIG 25 HYPERTROPHIC TYPE OF GRANULOMA INVOLVING MAJOR LABIA, CLITORIS, PERINEUM, AND PERI-ANAL REGION IN FEMALE



FIG 26 SCLEROTIC TYPE OF GRANULOMA IN MALE INVOLVING PENIS PENILE SHAFT AND INNER ASPECT OF BOTH GROINS



FIG 27 DESTRUCTIVE NECROTIC TYPE OF GRANULOMA INVOLVING EXTERNAL GENITALIA PERINEUM AND PERI ANAL REGION IN FEMALE



FIG 28 PSEUDO ELEPHANTIASIS OF PENIS SECONDARY TO HEALED DONOVANOSIS



FIG 29 PSEUDO ELEPHANTIASIS OF EXTERNAL GENITALIA IN FEMALE WITH LONG STANDING DONOVANOSIS



FIG 30 ALMOST COMPLETE OBLITERATION OF PUDENDAL CLEFT



FIG 31 COMPLETE DESTRUCTION OF PENIS SECONDARY TO DONOVANOSIS

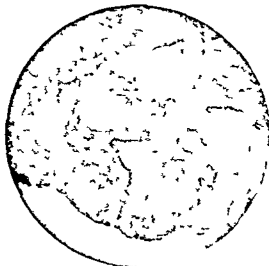


FIG 32. PSEUDO EPITHELIOMATOUS HYPERPLASIA GRADE II IN A CASE OF DONOVANOSIS



Low power photomicrog aph : marked acanthosis with tendency to pearl formation in spite of ir egular epithelial down-growths the integrity of basal layer is ma ntained abundant subepidermal inflammatory cells

FIG 33 PSEUDO EPITHELIOMATOUS HYPERPLASIA GRADE III IN A CASE OF DONOVANOSIS



Low power photomicrograph acanthosis but with ma kedly irregular and riotous down-growths of ep thel um with ind st nct and b urred basal layer : moderate subepide mal co lect ons of inflammatory cel s

FIG 34. EXTRAGENITAL GRANULOMA INGUINALE OF NECK







Note excellent response to antibiotics

By courtesy of Dr R B Greenblatt Medical College of Georgia, USA

FIG 25 EXTENSIVE GRANULOMA OF GROINS AND OF INGUINAL AND PUBIC REGIONS WITH DEFORMITY OF PENIS
(A) BEFORE AND (B) AFTER TREATMENT WITH STREPTOMYCIN





FIG 36 SUCCESSFUL TRANSPLANTATION OF CHEMORESISTANT DONOVANOSIS IN GROIN AND FORE ARM OF A VOLUNTEER

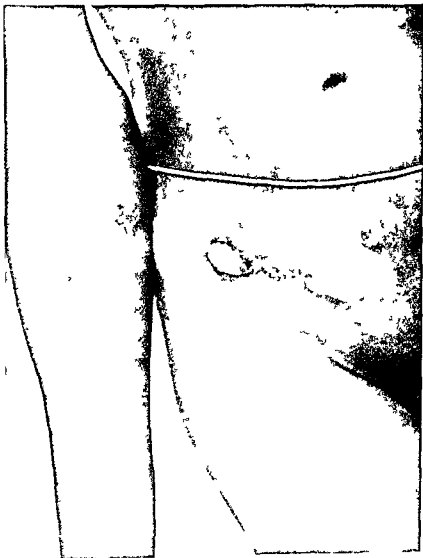


FIG 37 GRANULOMA INGUINALE OF CERVIX (OFTEN MISTAKEN FOR CERVICAL CARCINOMA) BEFORE TREATMENT WITH CHLORAMPHENICOL



By courtesy of Dr R B Greenblatt Medical College of Georgia USA

TREPONEMATOSES

A World Problem

T. Guthe & R. R Willcox

This publication tells the story of the progress made since the second World War in combating this group of infections

In a section dealing with changing concepts in the epidemiology and control of the treponematoses, the authors give a brief epidemiological history of the treponematoses, describe the nature and extent of the problem which these infections present today, and discuss the new methods for their control This is followed [illegible]

The booklet is abundantly illustrated with graphs, maps, and clinical photographs and includes a selective WHO bibliography on treponematosis control.

This publication is the first complete review of the present status of the treponematoses as a world health problem and should be of interest not only to treponematologists and venereologists, but also to the general public-health worker, to those interested in medical advances, and to all concerned with international co-operation in health activities

1954, 79 pages, 27 illustrations 3/6 $0 50 Sw fr 2.—

(This booklet is a reprint of a special number of the *Chronicle of the World Health Organization*, 1954, 8, 37 114)